Total Synthesis and Determination of the Absolute Configuration of Frondosin B

Masayuki Inoue,[†,§] Matthew W. Carson,[†] Alison J. Frontier,[‡,⊥] and Samuel J. Danishefsky*[,†,‡]

Contribution from the Laboratory for Bioorganic Chemistry, Sloan−Kettering Institute for Cancer Research, 1275 York Avenue, New York, NY 10021 and the Department of Chemistry, Columbia University, Havemeyer Hall, New York, NY 10027

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Abstract: Two concise syntheses of (±)-frondosin B (**1**), an interleukin-8 receptor antagonist, have been achieved from commercially available 5-methoxysalicylaldehyde. The seven-membered ring in ketone **33**, the common intermediate for both syntheses, was built by a classical Friedel−Crafts reaction. The key step of the first route was facile cationic cyclization of the vinylogous benzofuran to the trisubstituted olefin (**30** → **16** + **38**) to construct a six-membered carbocycle. Although this route demonstrated the efficacy of the stepwise approach to the frondosin ring-system, it also resulted in olefinic isomers that were easily isomerized in acidic conditions. In the second route, we utilized a Diels−Alder reaction between sterically demanding diene **42** and nitroethylene to fix the double bond in its required position in the resultant dimethylcyclohexane ring. A third total synthesis was devised for the purpose of determining the absolute configuration of frondosin B. It reached diene **42**, this time in the enantiomerically defined form. From this point, naturally configured frondosin B was obtained in the enantiomerically enriched form. These studies establish the absolute configuration of the secondary methyl center in frondosin B to be *R*.

Introduction

Interleukin-8 (IL-8), a chemoattractant for neutrophils, is produced by macrophages and endothelial cells.[1] IL-8 has been implicated in a wide range of acute and chronic inflammatory disorders, including psoriasis and rheumatoid arthritis.[2] Furthermore, various animal models of inflammation have established IL-8 as a principal chemotactic factor directing neutrophil recruitment to the inflammatory focus. Therefore, an IL-8 receptor antagonist represents a promising target for the development of novel pharmacological agents against autoimmune hyperactivity.

Frondosins A−D were recently isolated from the sponge *Dysidea frondosa*. Each of them inhibited the binding of IL-8 to its receptor in the low micromolar range.[3a] The structures of these compounds, which bear a casual relationship to one another, were determined mainly by NMR spectroscopy. Their unifying architectural theme is the presence of bicyclo[5.4.0]-undecane ring systems in the context of permuted linkages to various hydroquinone-based moieties.[4]

A National Cancer Institute (NCI) team also obtained frondosins A and D from the HIV-inhibitory organic extract of the marine sponge *Euryspongia* sp.[3b,5] It is worth noting that the frondosins, which were isolated at the NCI, exhibit opposite optical rotations with different absolute values in comparison to the previously isolated frondosins. Thus, the frondosins, except for frondosin B, are apparently fashioned by nature in both enantiomeric forms. It was anticipated that further biological studies of frondosins could spur fruitful investigations into IL-8 activity and present new possibilities for the development of novel antiinflammatory agents. These considerations, as well as the novel structure of the frondosins, prompted us to undertake a program directed toward their total synthesis.

In the opening phase of inquiry we focused on frondosin B (**1**)[3a], which contains an intriguing benzofuran ring system fused to a nor sesquiterpenoid (14-carbon) framework. In this paper, we report an account of a highly efficient total synthesis of this compound by three different routes.[6] The third reaches the naturally occurring enantiomer in 84% ee and establishes it to be of the *R* configuration. We first focused on frondosin B racemate as our goal. A number of "retrosynthetic disconnections" were employed in pursuing the racemate synthesis. Initially, we planned to couple two fragments by forming a bond between C6 and C7 then closing the seven-membered ring via a C10−C11 bond formation (Scheme 1). The union of the left and right domains can be envisioned as arising from the 1,4-addition of a suitably functionalized benzofuran **3** to the exocyclic enone, **2**.[7] We also took note of the possibility that

[†] Sloan−Kettering Institute for Cancer Research.

[‡] Columbia University.

[§] Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan.

[⊥] Department of Chemistry, Stanford University, Stanford, CA 94305.

(1) For a recent review of IL-8, see: Hock R. C.; Schraustätter I. U.; Cochrane C. G. *J. Lab. Clin. Med.* **1996**, *128*, 134.

(2) (a) Scitz, M.; Dewald, B.; Gerber, N.; Baggiolini, M. *J. Clin. Invest.* **1991**, *87*, 463. (b) Miller, E.; Cohen, A.; Nagos, S.; Griffith, D.; Maunder, T.; Martin, T.; Weiner-Kronish, J.; Sticherling, M.; Christophers, E.; Matthay, M. *Am. Rev. Respir. Dis.* **1992**, *146*, 427.

(3) (a) Patil, A. D.; Freyer, A. J.; Killmer, L.; Offen, P.; Carte, B.; Jurewicz, A. J.; Johnson, R. K. *Tetrahedron*, **1997**, *53*, 5047. (b) Hallock, Y. F.; Cardellina, J. H., II.; Boyd, M. R. *Nat. Prod. Lett.* **1998**, *11*, 153−160.

(4) For a recent review of marine sesquiterpene/quinone, see: Capon, R. J. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Science: New York, 1995; Vol. 15, p 289.

(5) Boyd, M. R. In *AIDS Etiology, Diagnosis, Treatment and Prevention*; DeVita, V. T., Jr., Hellman, S.; Rosenberg, S., Eds.; Lippincott: Philadelphia, 1988; p 305.

(6) For a preliminary account of this work, see: Inoue, M.; Frontier, A. J.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 761.

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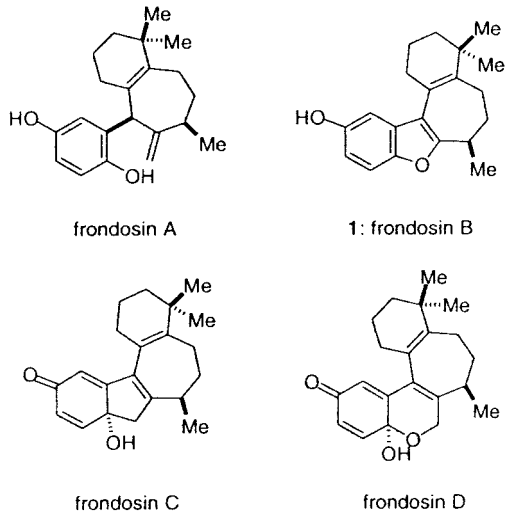
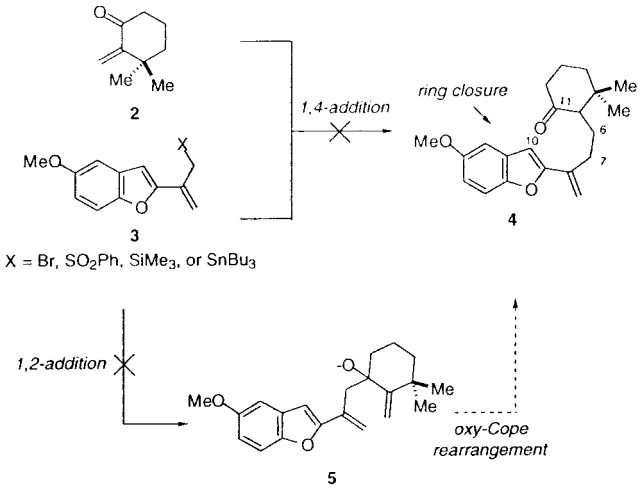


Figure 1.

Scheme 1. Nucleophilic Coupling Strategy

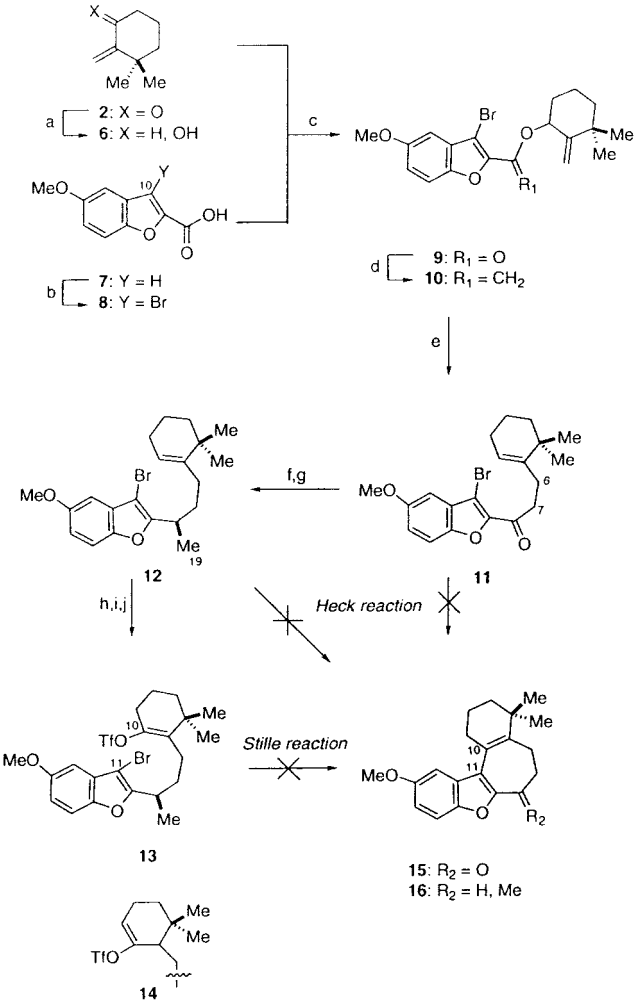


sequential 1,2-addition and oxy-Cope rearrangements could provide an alternative to the 1,4-addition pathway.

Following preparation of the benzofuran derivative **3**,[8] the first difficulty we encountered, even after screening numerous reaction conditions, was that neither 1,4- or 1,2- addition could be accomplished. Presumably, these difficulties reflect the steric demand of the *gem*-dimethyl group. Apparently, the trajectory for nucleophilic attack at the exocyclic methylene group incurs serious hindrance from the proximal quarternary center.

Accordingly, we modified the coupling strategy to rely on an intramolecular delivery modality. It was hoped that Claisen rearrangement of compound **10** could serve to create the elusive C6−C7 linkage (Scheme 2). To test this strategy, alcohol **6** was prepared by 1,2-reduction of ketone **2**[9] and compound **8** was synthesized by installation of bromine at C10 via the known carboxylic acid **7.**[10] The synthesis proceeded with the joining of the two domains by standard esterification of **8** with **6**. The resultant ester **9** was smoothly transformed to diene **10** using the Tebbe reagent.[11] Gratifyingly, subsequent heating gave,

Scheme 2.[a] Claisen Rearrangement Strategy



[a] Reagents and conditions: (a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C, >90%; (b) Br_2, CS_2, reflux, 24 h, >90%; (c) **8**, TsCl, pyridine, then **6**, 78%; (d) Tebbe reagent, benzene, 0 °C to room temperature; (e) 80 °C, PhMe, 30 min, 82% (2 steps); (f) MeMgBr, 0 °C, 78%; (g) $NaCNBH_3$, ZnI_2, 86%; (h) $BH_3 \cdot Me_2S$, H_2O_2, NaOH; (i) Jones reagent, 37% (2 steps); (j) Tf_2O, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, reflux, 81% (**13**:**14** = 2:3).

cleanly, the Claisen rearrangement product **11** in good yield.[12] The ketone in **11** was converted to the required C19 methyl function in two steps. Thus, addition of methylmagnesium bromide, followed by reduction of the resultant carbinol with sodium cyanoborohydride in the presence of anhydrous zinc iodide as the Lewis acid,[13] provided compound **12** in good yield.

Having successfully constructed the desired functionality, we undertook a series of initiatives aimed at achieving ring closure. A Heck reaction[14] was attempted first as we began to evaluate the applicability of palladium chemistry in this series. Experiments were conducted on bromides **11** and **12**. No cyclization was observed under the various conditions we employed. We then focused our attention on Stille-type reactions. Installation of a ketone at C11 was achieved by hydroboration of **12** and

(7) (a) White, J. D.; Skeean, G. L.; Trammell, G. L. *J. Org. Chem.* **1985**, *50*, 1939. (b) Adams, J.; Lepine-Frennette, C.; Spero, D. M. *J. Org. Chem.* **1991**, *56*, 4494.

(8) For an account of the many adversities arising from earlier efforts, see: Frontier A. J.; Ph.D. Thesis, Columbia University, 1999.

(9) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226. (b) Luche, J.-L.; Rodriquez-Hahn, L.; Crabbé, P. *J. Chem. Soc., Chem. Commun.* **1978**, 601.

(10) Tanaka, S. *J. Am. Chem. Soc.* **1951**, *73*, 872.

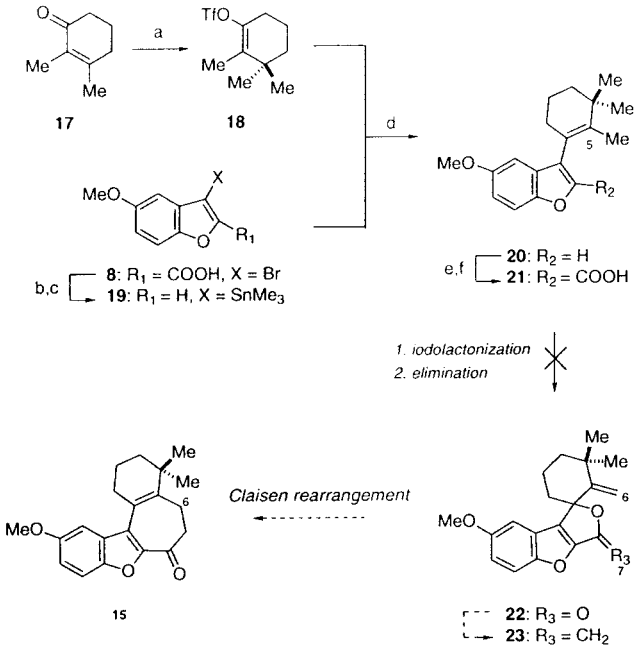
(11) Tebbe, F. N.; Marshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611.

(12) Kinney, W. A.; Coghlan, M. J.; Paquette, L. A. *J. Am. Chem. Soc.* **1985**, *107*, 7352.

(13) Lau, C. K.; Dufresne, C.; Bélanger, P. C.; *J. Org. Chem.* **1986**, *51*, 3038.

(14) For excellent reviews, see: (a) Heck, R. F. *Palladium Reagents in Organic Syntheses*; Academic Press: New York, 1985; p 179. (b) Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379.

Scheme 3[a]



[a] Reagents and conditions: (a) Me_2CuLi, −78 °C to 0 °C, then Comins Reagent, 55%; (b) Cu, quinoline, 220 °C, 70%; (c) *n*-BuLi, −20 °C, 2 h, then Me_3SnCl, 0 °C to room temperature, 70%; (d) 2.5 mol % $Pd_2(dba)_3$, 6 equivs LiCl, *N*-methylpyrrolidine, 50 °C, 23−34%; (e) $POCl_3$, DMF, $(CH_2Cl)_2$, reflux, 5h, 36% (65% BORSM); (f) $AgNO_3$, aq NaOH, 75%.

subsequent Jones oxidation. Enol triflation of the ketone with Tf_2O in the presence of base gave an ∼2:3 mixture of **13** and **14** (Scheme 2). Separation of these components proved to be very difficult. Because a variety of conditions failed to improve the selectivity of this triflation, we resorted to using the unseparated mixture for the projected C10−C11 ring-closure. Unfortunately, attempted palladium-catalyzed Stille reactions of this material under various conditions were unsuccessful.[15] In several instances, spectroscopic examination of the recovered material suggested that the tetrasubstituted triflate had survived intact.

These disappointing results underscored the need for a fresh approach. The previous Claisen bond reorganization pathway, which was actually quite promising in the rearrangement step, had to be abandoned because of our inability to achieve intramolecular merger between carbons 10 and 11. Our next plan was to alter the sequence of events by first forming the C10−C11 linkage through intermolecular means (Scheme 3). A subsequent Claisen rearrangement of compound **23** was planned with a view to building the seven-membered ring through construction of a C6−C7 bond.[16] The appropriately functionalized components were assembled. Thus, the known **17**[17] was treated with lithium dimethyl cuprate. The resultant enolate was trapped with Comins reagent[18] to provide the triflate **18**. Decarboxylation of **8**, followed by lithiation and stannylation, led to the required stannane **19**.

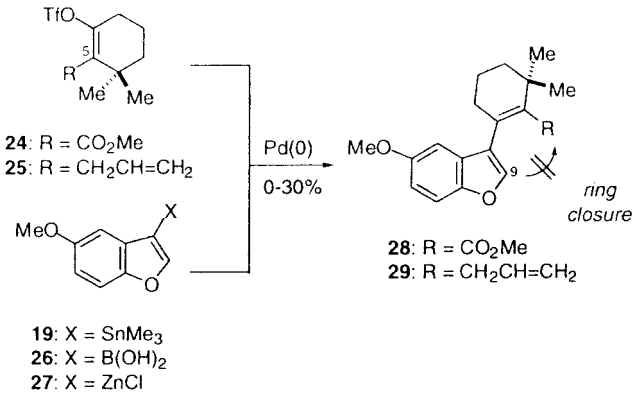
(15) For successful applications of related Stille-type reactions, see: (a) Kelly T. R.; Li Q.; Bhushan V. *Tetrahedron Lett.* **1990**, *31*, 161. (b) Grigg, R.; Teasdale, A.; Sridharan, V. *Tetrahedron Lett.* **1991**, *32*, 3859. (c) Mori, M.; Kaneta N.; Shibasaki, M. *J. Org. Chem.* **1991**, *56*, 3486. (d) Huang, A. X.; Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 9999.

(16) (a) Marvell, E. N.; Titterington, D. *Tetrahedron Lett.* **1980**, *21*, 2123. (b) Ovaska, T. V.; Roark, J. L.; Shoemaker, C. M.; Bordner, J. *Tetrahedron Lett.* **1998**, *39*, 5705.

(17) Jung, M. E.; McCombs, C. A.; Takeda, Y.; Pan, Y.-G. *J. Am. Chem. Soc.* **1981**, *103*, 6677.

(18) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.

Scheme 4



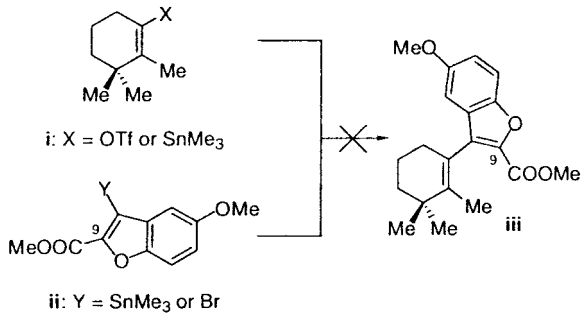
When the coupling of **18** and **19** was conducted under ligandless conditions, as recommended for sterically demanding substrates,[19] the adduct was isolated in modest yield.[20] In this reaction, substantial amounts of 3-methoxybenzofuran were obtained. Installation of a carboxylic acid at C9 was achieved by a two-step procedure. Vilsmeier formylation[21] successfully introduced the aldehyde. Following oxidation,[22] compound **21** was in hand. Our plan included activation of the tetrasubstituted alkene in order to effect halolactonization. Unfortunately, the lactonization could not be achieved. We took this disappointing result to reflect the difficulties of attack by a viable iodonium equivalent at C5, even in the presence of a proximal, and presumably participating, carboxylate function. This negative outcome provided further testimony to the high risks in attempting to conduct chemistry proximal to the gem-dimethyl quarternary center.

Even as these unsuccessful efforts were in progress, efforts directed toward an alternative construction of the seven-membered ring were initiated (Scheme 4). The methyl ester vinyl triflate **24** and allyl-substituted vinyl triflate **25** were synthesized as shown. However, merger of **24** or **25** with activated benzofuran (**19**, **26**, or **27**) using palladium(0) as a catalyst[23] was low-yielding and unreliable. The coupling yields deteriorated still further when the reaction was conducted on scales larger than a few milligrams. Because we were unable to solve this material availability problem, progress was severely hindered, and this initiative was also abandoned.

The series of negative results described above, augmented by many others,[8] underscored several important points: First, bond formation in spatial proximity to the dimethyl group was

(19) Farina, V.; Roth, G. P. *Tetrahedron Lett.* **1991**, *32*, 6299.

(20) We also attempted Stille reactions on the C9 functionalized benzofuran. However, none of the desired adduct **iii** was isolated.

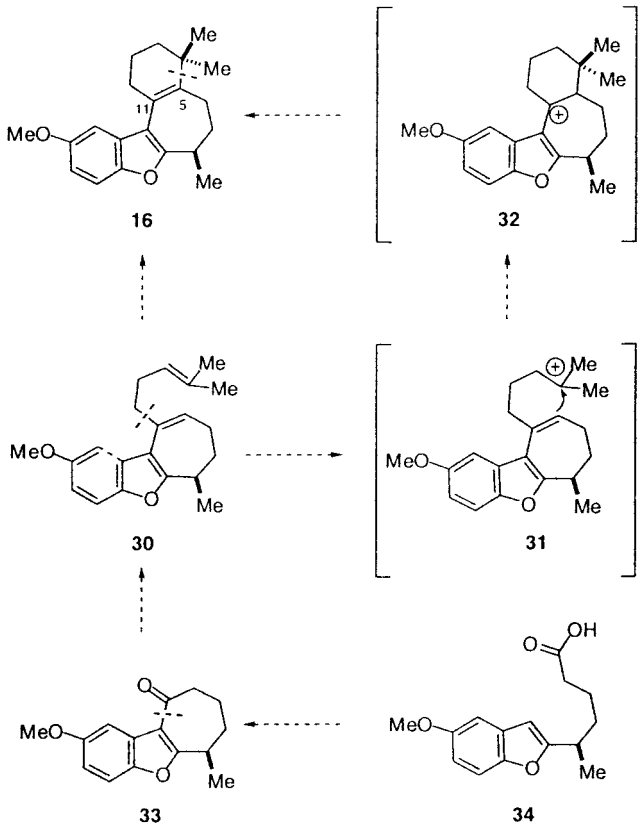


(21) For a recent review of the Vilsmeier reaction, see: Jones G. *Org. React.* **1997**, *49*, 1.

(22) Sharmma, M.; Rodrigues, H. R. *Tetrahedron* **1968**, *24*, 6583.

(23) For a review of coupling between sp^2 carbon centers, see: Knight D. W. In *Comprehensive Organic Synthesis*; Trost B. M., Fleming I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, p 481.

Scheme 5



emerging as rather difficult and would be particularly risky with advanced intermediates. Furthermore, attachment of tetrasubstituted olefin derivatives to the β-position of the furan (corresponding to C10 of the target frondosin) by organometallic methods, appears to be highly problematic.

With these considerations in mind, we developed a totally revised approach to the problem. The new perception involved incorporation of the cyclohexene ring containing the gem-dimethyl group onto a preexisting matrix wherein the seven-membered ring was already in place (Scheme 5). More specifically, in this stepwise approach, the seven-membered ring diene **30** would be synthesized by addition of a homoprenyl group to a ketone such as **33**. This bond formation would set the stage for subsequent acid-induced cyclization, exploiting the activated benzofuran ring to promote and guide the sense of electrophilic attack on the cycloheptenyl double bond (see **30** → **16**).[24] We hoped that the tetra-substituted olefin between C5 and C11 would be markedly more stable than trisubtituted isomers and could accordingly be generated under equilibrating conditions.[25]

The synthesis started from the acetyl benzofuran **35**, which was prepared from 2-hydroxy-5-methoxy benzaldehyde by the known protocol,[26] shown in Scheme 6. Four-carbon extension of **35** by Wittig methodology proceeded smoothly to give olefin **37** (*Z*:*E* = 3:2) in 87% yield.[27] The olefin in **37** was hydrogenated using palladium on carbon. Subsequent saponification furnished carboxylic acid **34** in quantitative yield. In the hydrogenation step, extended reaction times resulted in formation of significant quantities of dihydrobenzofuran. Fortunately, the critical Friedel−Crafts reaction could be accomplished. Thus, reaction of **34** with oxalyl chloride and treatment of the resultant acid chloride with stannic chloride gave ketone **33** in good yield.[28]

Nucleophilic attack of the cerium reagent,[29] prepared from 4-methyl-3-pentenylmagnesium bromide, led to an addition product. Dissolution of the resultant tertiary alcohol in chloroform afforded the diene **30** as a 5:1 mixture with its endo isomer in 93% yield. The remarkable susceptibility of the tertiary alcohol to dehydration presumably arises from participation of the benzofuran in stabilizing an intermediate bearing cationoid character. Fortunately, acid-induced cyclization of **30** proceeded under mild conditions in reasonable yield. Various acid combinations (BF_3·OEt_2, HCOOH, H_3PO_4,) resulted in the formation of the six-membered ring in an approximately 2.5:1 mixture favoring the desired compound **16** and olefinic isomer mixture **38**. Mercury trifluoroacetate-mediated reaction,[30] in which olefin isomerization after cyclization was expected to be minimal, also proceeded smoothly. Unfortunately, following reductive cleavage of the carbon−mercury bond, very similar isomeric ratios were obtained. The results of these reactions suggested that the product distribution might be reflecting the thermodynamic stability order of rapidly equilibraiting isomers. However, there remains the possibility that the nonvariant ratio could arise from kinetic factors.

Although these isomers were inseparable by silica gel chromatography, we attempted to complete the total synthesis, hoping for a later-stage separation (Scheme 6). Deprotection of the methyl ether was effected with boron tribromide to afford (±)-frondosin B (**1**) and its olefinic isomers **39** in 87% yield. These isomers were separated with HPLC (silica gel, 5% ethyl acetate−hexane). The ^{1}H, ^{13}C NMR and IR spectra obtained from synthetic frondosin B were identical with those reported from the naturally occurring material.[31] Thus, the total synthesis of racemic frondosin B has been achieved in 9 steps from commercially available 2-hydroxy-5-methoxybenzaldehyde. Although this synthesis is highly concise and ensures quick access to reasonable amounts of material, the unsolved problem associated with control over the regiochemistry of olefin formation still remained irksome and prompted a fresh approach.

We noted that subjection of **1** and **39** separately to a variety of acidic conditions led to formation of a 2.5:1 mixture of the same products (Scheme 6). These data seemed to confirm that the mixture of double-bond isomers (**16** and **38** or **1** and **39**). Accordingly, to achieve control in our synthesis, it would be necessary to construct the dimethylcyclohexene from **33** without recourse to acidic catalysis in the formation of the fully mature A ring or after its construction.

(24) For a review of cationic cyclizations, see: (a) Bartlett P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol 3, pp 341. (b) Sutherland, J. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol 3, p 341.

(25) It is known that a double bond can generally be fixed on the most substituted position in a Decalin system using acidic conditions. For example, see: Ayer, A. W.; Hellou, J.; Tischler, M.; Andersen, R. J. *Tetrahedron Lett*, **1984**, *25*, 141.

(26) Landelle, H.; Godard, A. M.; Laduree, D.; Chenu, E.; Robba, M. *Chem. Pharm. Bull.* **1991**, *39*, 3057.

(27) Danheiser, R. L.; Halgason, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 9471.

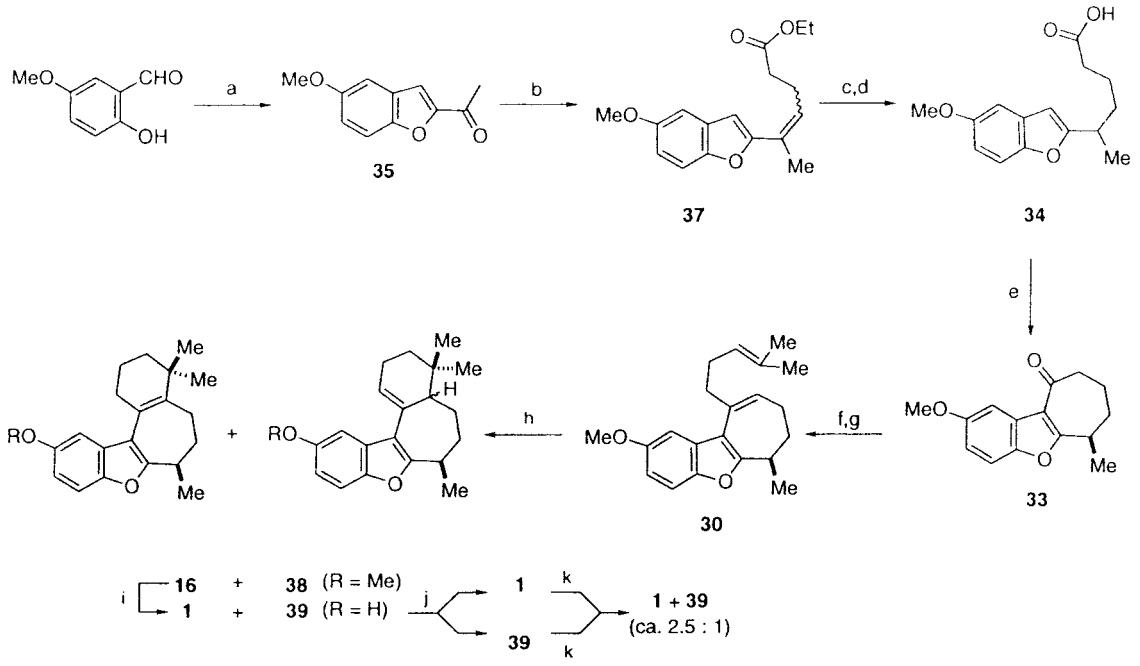
(28) Friedel−Crafts cyclization to benzofuran is relatively rare. For an example leading to a six-membered ring, see: Bhide, G. V.; Tikotkar, N. L.; Tilak, B. D. *Tetrahedron* **1960**, *10*, 223−229.

(29) (a) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392. (b) Fujiwara, T.; Iwasaki, T.; Takeda, T. *Chem. Lett*. **1993**, 1321. (c) Guevel, A. C.; Hart, D. J. *J. Org. Chem*. **1996**, *61*, 465.

(30) (a) Kurbanov, M.; Semenovsky, A. V.; Smit, W. A.; Shmelev, L. V.; Kucherov, V. F. *Tetrahedron Lett*. **1972**, *22*, 2175. (b) Corey, E. J.; Tius, M. A.; Das, J. *J. Am. Chem. Soc*. **1980**, *102*, 1742. (c) Sato, C.; Ikeda, S.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1982**, *23*, 2099.

(31) We note that direct comparison of synthetic racemate and material product was not possible because a specimen of natural frondosin furnished to us reached our lab in a totally decomposed and unrecognizable state.

Scheme 6.[a] Cationic Cyclization Strategy



[a] Reagents and conditions: (a) chloroacetone, K_2CO_3, 2-butanone, 80 °C, 72%; (b) $Br^-Ph_3P^+(CH_2)_3CO_2Et$ (**36**), $NaN(SiMe_3)_2$, THF, 0 °C to room temperature, 87% (*Z*:*E* = 3:2); (c) H_2, Pd/C, EtOH, room temperature; (d) LiOH, THF−MeOH−H_2O, 100% (2 steps); (e) $(COCl)_2$, CH_2Cl_2, reflux, then $SnCl_4$, −78 °C to −10 °C, 67%; (f) 4-methyl-3-pentene magnesium bromide, $CeCl_3$, THF, −78 °C; (g) $CDCl_3$, 93% (2 steps, endo:exo = 5:1); (h) $BF_3{\cdot}Et_2O$, MeCN, room temperature, 81%, (**16**:**38** = 2.5:1); (i) BBr_3, CH_2Cl_2, −78 °C to room temperature, 98%, (**1**:**39** ≈ 2.5:1); (j) HPLC separation (silica gel, 5% ethyl acetate−hexane); (k) *p*-TsOH, PhH, 80 °C.

Given these constraints, which were by now well appreciated, we modified the synthetic route to attain a completely regiocontrolled outcome. To install the double bond at the proper C5−C11 position without the requirement for acidic conditions, we came to favor a Diels−Alder-inspired logic to form the C1−C2 and C3−C4 bonds.[32] Accordingly, construction of the corresponding diene (see structure **42**) was initiated via the aldol condensation of ketone **33** with acetone (Scheme 7). The zinc enolate of the ketone, prepared by transmetalation of the lithium enolate, reacted with acetone to furnish adduct **40** in 85% yield.[33] Not surprisingly, this compound was prone to retro-aldolization, especially in acidic media. Indeed, treatment of **40** with *p*-toluenesulfonic acid produced ketone **33** in 77% yield along with a trace amount of olefin **41**. After several experiments, dehydration of the tertiary alcohol was accomplished by treatment of **40** with mesyl chloride and triethylamine. This protocol gave rise to a mixture of olefinic isomers (∼1:1) in 88% yield. Treatment of this mixture of sodium methoxide in methanol effected isomerization of the $\beta-\gamma$ unsaturated olefin tautomers to provide the desired compound **41** in 96% yield.[34] Finally, diene **42** was prepared in 97% yield following exposure of **41** to the Tebbe reagent[11] buffered with pyridine.

As was noted in preliminary reconnaissance experiments, compound **42** is sensitive to acid. In addition, it is relatively unreactive. However, reaction of **42** with maleic anhydride at 110 °C for 2 days did give a Diels−Alder adduct, albeit in only 27% yield.[35] Considering the acid-sensitivity of **42** as well as the expected tendency toward olefin migration of the product, a Lewis acid-promoted Diels−Alder reaction would be problematic. Accordingly, we elected to use nitroethylene as a reactive ethylene equivalent under acid-free conditions.[36] It was expected that the nitro group could be easily removed through a free radical protocol. In addition, it was anticipated that the nitro group might actually be useful for synthesizing structural analogues for biological investigations.

Diels−Alder reaction of **42** with excess nitroethylene in the presence of di-*tert*-butyl pyridine at 80 °C afforded adduct **43** in 79% yield. The nitro group was removed by radical reduction to afford *O*-methyl frondosin B **16** in 58% yield.[37] Finally, synthesis of geometrically pure frondosin B (**1**) was achieved by deprotection of the methyl group, this time with sodium ethanethiolate (94%).[38] In this alternative route, the total synthesis of (±)-frondosin B was realized in 12 steps. The method clearly has potential for the synthesis of numerous structural variants.

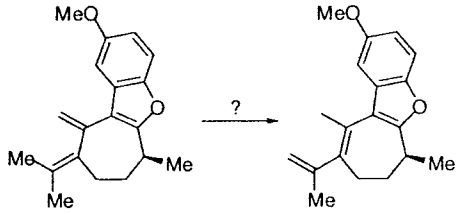
Having completed the synthesis of racemic frondosin B, we embarked on an enantio-defined preparation of the natural product. The goal was not only to gain access to the naturally occurring enantiomer but also included determination of the absolute configuration of frondosin B. We would start with a chiral precursor of known absolute configuration and use it to

(32) For a related Diels−Alder reaction producing a Decalin system, see: Omodani T.; Shishido, K. *Chem. Commun*. **1994**, 2781.

(33) (a) Hagiwara, H.; Uda, H.; Kodama, T. *J. Chem. Soc., Perkin Trans. 1* **1980**, 963. (b) Witschel, M. C.; Bestmann, H. J. *Synthesis* **1997**, 107.

(34) Guerriero, A.; Cuomo, V.; Vanzanella, F.; Pietra, F. *Helv. Chim. Acta*. **1990**, *73*, 2090.

(35) Side-reactions could involve acid-catalyzed 1,5-proton shift cycloadditions or ene-reactions with maleic anyhydride.

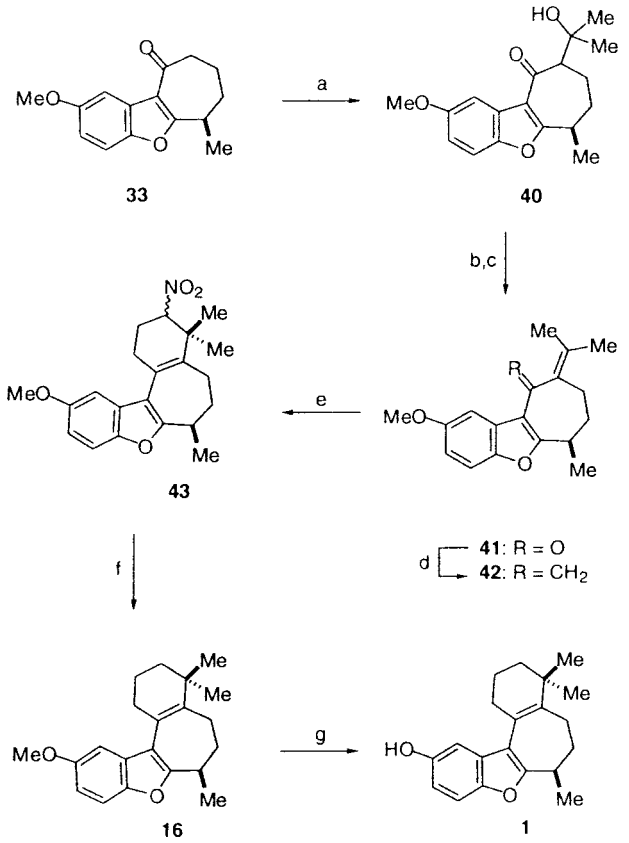


(36) (a) Ranganatham, D.; Rao, C. B.; Ranganatham, S.; Mehrotra, A. K.; Iyengar, R. *J. Org. Chem.* **1980**, *45*, 1185. (b) Corey, E. J.; Myers, A. G. *J. Am. Chem. Soc*. **1985**, *107*, 5574.

(37) Ono, N.; Kaji, A. *Synthesis* **1986**, 693.

(38) Feutrill, G. I.; Mirrington, R. N. *Aust. J. Chem*. **1972**, *25*, 1719.

Scheme 7.[a] Diels−Alder Strategy



[a] Reagents and conditions: (a) $LiN(SiMe_3)_2$, $ZnCl_2$, acetone, THF, −78 °C to −40 °C, 81% (96% BORSM); (b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 88%; (c) NaOMe, MeOH, 0 °C, 96%; (d) Tebbe reagent, pyridine, THF, −40 °C, 97%; (e) excess nitroethylene, di-*tert*-butyl pyridine, 80 °C, 79% (5:1 mixture of diastereomers); (f) tri-*n*-butyltin hydride, AIBN, PhMe, 110 °C, 58%; (g) NaSEt, DMF, reflux, 94%.

reach either frondosin B or the enantiomer of frondosin B. In either case, we would have answered our question. Because the Diels−Alder route (Scheme 7) had provided racemic frondosin B in a regio-controlled fashion, benzofuran **34**, an intermediate in the synthesis of the racemate, appeared to be a reasonable target (Scheme 8). The annulation between alkyne **44** and 4-methoxy-2-iodophenol (**45**) to afford an enantio-enriched 2-substituted benzofuran system would then serve as one of the key steps in synthesis.

With this program in mind, a method for enantioselectively installing the secondary methyl group was required. Prior work[39] had shown that treatment of 2,3-epoxy alcohols with $AlMe_3$ results in the regioselective ring opening of epoxides to give 3-methyl-1,2-diols. Thus, we felt that the Sharpless asymmetric epoxidation [40] of a prochiral alcohol followed by C-methylation of the epoxy alcohol via $AlMe_3$ would serve as a highly regio- and stereoselective method for introducing the secondary methyl group and could ultimately lead to enantio-enriched alkyne **44**.

As shown in Scheme 9, the synthesis of (+) frondosin B (**1**) commenced with the epoxidation of the known methyl 7-hydroxy-5-(*E*)-heptanoate (**46**)[41] with *tert*-butyl hydroperoxide using catalytic $TiCl_4$ and (+)-diisopropyl-L-tartrate gave (−)-methyl 5-(*S*), 6-(*S*)-epoxy-7-hydroxyheptanoate (**47**)[40a] in 63% yield, although only in 84% enantiomeric excess (ee). Low-temperature ring opening of epoxy alcohol **47** with excess $AlMe_3$ provided (+)-methyl 6-(*R*), 7-dihydroxy-5-(*R*)-methyl heptanoate (**48**) in 60% yield with >95% diasteromeric excess (de).[42] Periodate-induced cleavage of **48** yielded crude 5-(*R*)-methyl-6-oxohexanoate, which was converted smoothly to alkyne **44** by treatment with potassium dimethyl(methyl)-phosphonate (Gilbert reagent).[43] Potassium dimethyl(methyl)-phosphonate seemed to be a suitable reagent for the preparation of α-chiral aldehydes, as was shown in our recent synthesis of (−)-halichlorine.[44] The preparation of 2-iodo-4-methoxyphenol (**45**) was straightforward (Scheme 10). **45** was generated via directed ortho-lithiation[45] of the diethyl carbamate of 4-methoxy-1-phenol (**49**) followed by removal of the carbamoyl group.

With alkyne **44** and iodophenol **45** in hand, we directed our efforts toward the synthesis of the benzofuran framework. There have been a number of reports on the palladium-catalyzed heteroannulation of acetylenic compounds. Recently, Botta and Corelli[46] have expanded on existing protocols and have shown that either chiral propargylamines or alcohols undergo heteroannulations with 2-iodophenol, in the presence of catalytic $PdCl_2(PPh_3)_2$ and CuI, as well as tetramethylguanidine (TMG) at 40 °C, to give homochiral 2-benzofuranyl carbamines or carbinols, respectively, in good yields (60−80%). Unfortunately, in our case, under these conditions described, the reaction of 2-iodo-4-methoxyphenol (**45**) with (−)-methyl 5-(*R*)-methyl-6-heptynoate (**44**) gave 2-substituted benzofuran (−)-**50** in low yields (20−40%), along with apparent decomposition products (Table 1, entry 1). In hopes of circumventing the problem of decomposition, the reaction was conducted at room temperature and using the slightly stronger amine base piperidine.[47] As shown in Table 1 (entry 2), by carrying out the reaction at room temperature, the internal alkyne (−)-**51** was generated as the principal product (57%) and benzofuran (−)-**50** was produced in only 20% yield. When the reaction was run under conditions reported by Kundu[48] (catalytic $PdCl_2(PPh_3)_2$ and CuI; 2 equivs triethylamine, 25 °C, then 50 °C), alkynyl phenol (−)-**51** was produced in good yield (74%) along with only a trace amount of the desired product, (−)-**50** (Table 1, entry 3). With these results in mind, we focused our efforts on optimizing the Sonogashira coupling reaction between iodophenol **45** and alkyne (−)-**44** to provide alkynyl phenol (−)-**51**. To this end, (−)-**51** was isolated in excellent yield (93%) when the reaction was conducted under Kundu conditions at *room temperature only* (Table 1, entry 4). Finally, it was found that the cyclization

(39) (a) Rousch, W. R.; Adam, M. A.; Peseckis, S. M. *Tetrahedron Lett.* **1983**, *24*, 1377. (b) Suzuki, T.; Saimoto, H.; Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 3597. (c) Miyashita, M.; Hoshino, M.; Yoshikoshi, A. *J. Org. Chem.* **1991**, *56*, 6484.

(40) (a) Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 464. (b) Hill, J. G.; Sharpless, K. B.; Exon, C. M.; Regenye R.; *Organic Syntheses*; Wiley: New York, 1990; Coll. Vol. VII, p 461. (c) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922. (d) Hill, J. G.; Rossiter, B. E.; Sharpless, K. B. *J. Org. Chem.* **1983**, *48*, 3607. (e) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5976. (f) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.

(41) Prepared according to the general method reported by Patterson, J. W. *Synthesis* **1985**, 337.

(42) It should be noted that when epoxy alcohol **47** was treated with $AlMe_3$ at temperatures greater than ca. −50 °C, an apparent intramolecular ring opening of the epoxide by the attack of the carbonyl oxygen competed with intermolecular methylation.

(43) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1979**, *44*, 4997.

(44) Trauner, D.; Schwartz, J. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3542.

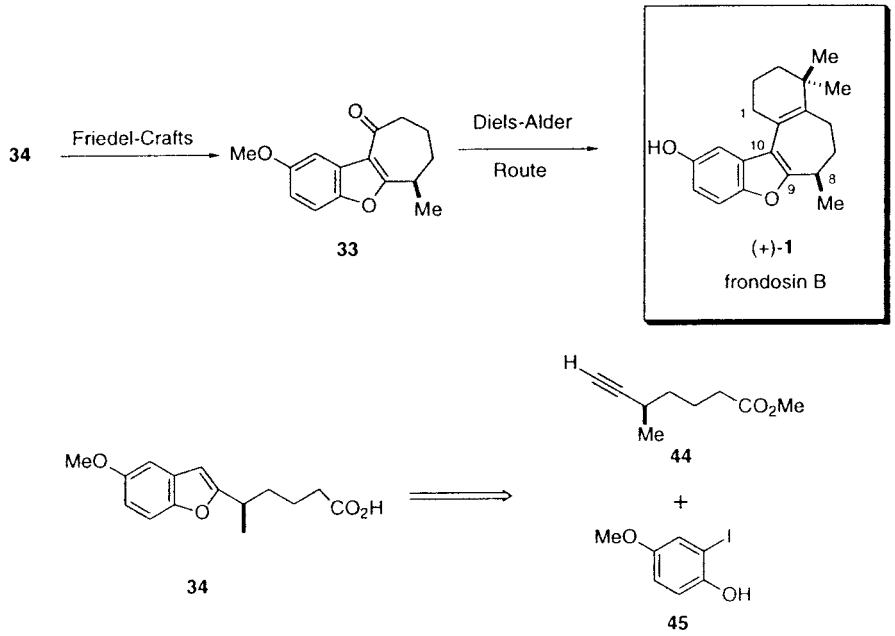
(45) (a) Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1983. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(46) (a) Messina, F.; Botta, M.; Corelli, F.; Mugnaini, C. *Tetrahedron Lett.* **1999**, *40*, 7289. (b) Botta, M.; Summa, V.; Corelli, F.; Di Pietro, G.; Lombardi, P. *Tetrahedron: Asymmetry* **1996**.

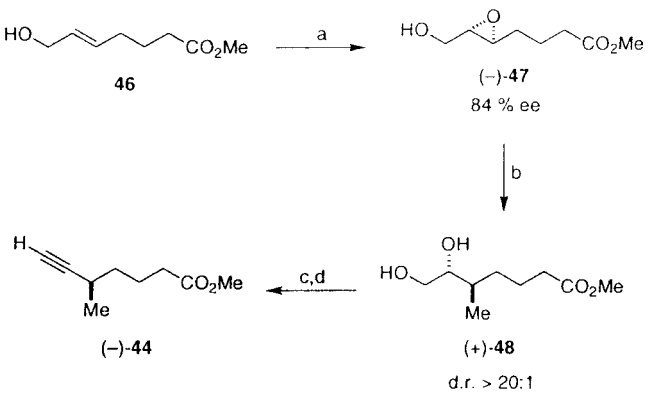
(47) (a) Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli F. *J. Org. Chem.* **1996**, *61*, 9280. (b) Arcadi, A.; Marinelli F. *Synthesis* **1986**, 749.

(48) Kundu, N. G.; Pal, M.; Mahanty, J. S.; Dasgupta, S. K. *J. Chem. Soc. Chem. Commun.* **1992**, 41.

Scheme 8

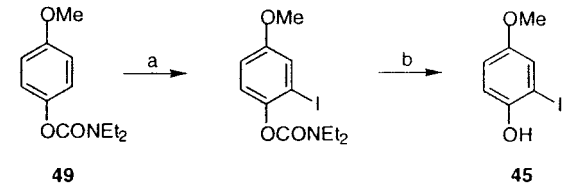


Scheme 9[a]



[a] Reagents and conditions: (a) TBHP−PhMe, Ti(*i*-PrO)$_4$, (+)-L-DIPT, CH_2Cl_2, −15 °C, 63%; (b) $AlMe_3$, CH_2Cl_2−hexane, −78 °C, 3 days, 60%; (c) $NaIO_4$, THF:H_2O; (d) $N_2CHPO(MeO)_2$, *t*-BuOK, THF, −78 °C to −50 °C, 71% (2 steps).

Scheme 10[a]



[a] Reagents and conditions: (a) *sec*-BuLi, THF−*c*-C_6H_6, −78 °C, 1.5 h then I_2−THF, −78 °C; (b) 2 N NaOH, MeOH, reflux, 4 days, 50% (2 steps).

of (−)-**51** proceeded smoothly to give (−)-**50** in 62% yield under Kundu conditions at 50 °C (Scheme 11).

At this point, the asymmetric synthesis nominally intersected with the racemic synthesis of frondosin B when 2-substituted benzofuran (−)-**50** was converted to carboxylic acid (−)-**34** by saponification. Under identical conditions previously described (Scheme 6), ketone (−)-**33** was furnished in good yield via the intramolecular Friedal-Crafts acylation of the acyl chloride that was derived from carboxylic acid (−)-**34**. Chiral stationary phase (CSP) HPLC analysis of the material revealed that (−)-**33** had been prepared in 84% ee.

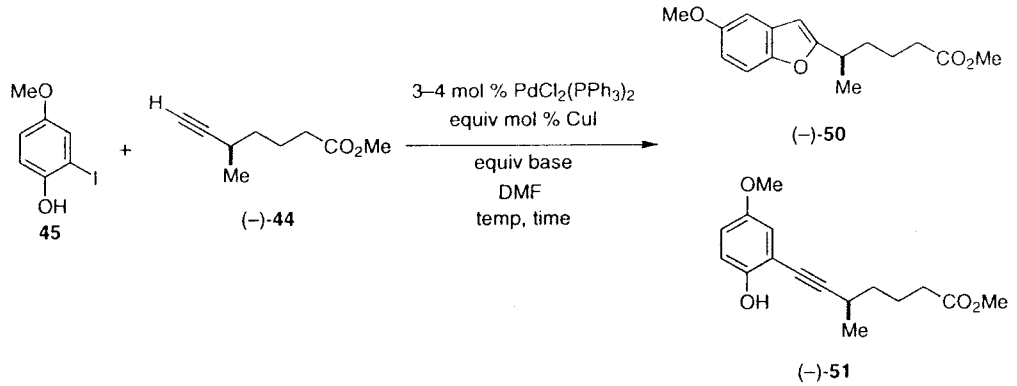
Because we were concerned with the possibility of racemization at the C8 chiral center, we were forced to proceed cautiously in our approach to the condensation of the enolate of ketone (−)-**33** with acetone. As shown in Scheme 12, a control experiment revealed that the lithium enolate of (−)-**33** could be formed almost quantitatively without racemization at C8. This was evidenced by the fact that the reaction of (−)-**33** with 1 equiv of LiHMDS, followed by MeOD quench, gave recovered (−)-**33** exclusively with 95% incorporation of deuterium at C5. Aldol condensation between the zinc enolate of (−)-**33**, prepared from the lithium enolate, and acetone gave alcohol **40** in 55% yield along with ketone **33** in 45% yield. However, recovered ketone (−)-**33**, most likely regenerated via a retro-aldol reaction, had a 24% ee (Scheme 12). Future studies would show that the C8 center in **41** was most likely racemized as well (vide infra). The racemization at the C8 center is probably due to the excess base remaining after the formation of the enolate of (−)-**33**. Deprotonation at C8 of the zinc chelate of **40** may serve as the racemization step. Unfortunately, the aldol product **40** was generated in low yields when only 1 equiv of LiHMDS was used. Gratifyingly, though, the problems of racemization and the retro aldol reaction were circumvented by generating the silyl enol ether of (−)-**33** in situ.[49] As depicted in Scheme 12, (+)-**52** was then smoothly transformed to tertiary alcohol **40** without epimerization at C8 (60% de) in 70% yield by the Mukaiyama reaction.[50]

Unfortunately, the dehydration of **40** resulted in another setback. As in the synthesis of the racemate (Scheme 7), conversion of **40** to its mesyl ether, followed by elimination, provided ∼1:1 mixture of olefinic isomers (Scheme 13). However, treatment of the olefinic isomers with sodium methoxide in methanol delivered olefin **41** exclusively as its racemate. In a parallel experiment with MeOD as the solvent, ^{1}H NMR analysis revealed that **40** was partially deuterated

(49) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.

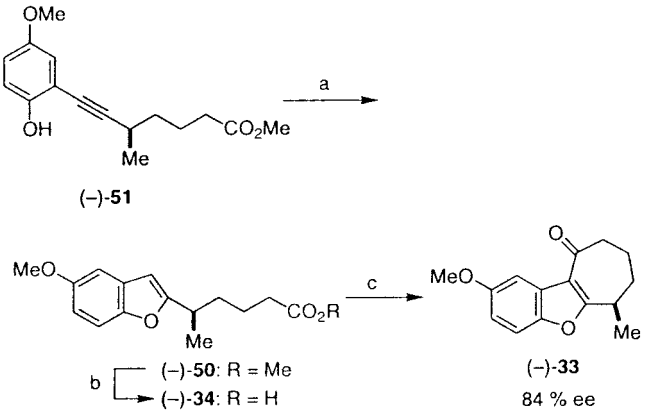
(50) (a) Mukaiyam, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503. (b) Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 817. (c) Mukaiyama, T. *Org. React.* **1982**, *28*, 203.(d) Banno, K.; Mukaiyama, T. *Chem. Lett.* **1976**, 238−240.

Table 1. Palladium (II)-Catalyzed Reactions between 4-Methoxy-2-iodophenol (**45**) and Methyl (−)-5(*R*)-6-heptynoate (**44**)



					products, % yield	
entry	mol % CuI	equiv base	temp °C	time h	(−)-**50**	(−)-**51**
1	2.7	3 .0 TMG	40	4	20−40	0
2	5.0	1.0 piperidine	25	48	20	57
3	13.4	2.0 NEt_3	25−50	48	5	74
4	13.4	2.0 NEt_3	25	24	3	93

Scheme 11[a]



[a] Reagents and conditions: (a) $PdCl_2(PPh_3)_2$, CuI, NEt_3, 50 °C, 62% (b) LiOH, THF−MeOH−H_2O, 25 °C, 99%; (c) $(COCl)_2$, CH_2Cl_2, 25−40 °C then $SnCl_4$, −78 °C to −10 °C, 62%.

(50%-d_1) at C8. Given this outcome, the dehydration of **40** was repeated and the mixture of olefinic isomers was carefully separated via column chromatography to give the desired **41** in 35% yield (84% ee) along with its geometric isomer (40%). A separate study showed that $PdCl_2(MeCN)_2$ in refluxing benzene effected isomerization of the olefinic mixture to **41** in 93% yield without further racemization.[51]

As shown in Scheme 14, the completion to the synthesis of (+)-frondosin B (**1**) was accomplished in a fashion analogous to that employed for (±) frondosin B. Analyses indicated that (+)-frondosin B (**1**) had been generated in approximately 84% ee with an optical rotation of +15.2°. The literature reports that pure (+)-frondosin B has an optical rotation of +18.5°.[3] Because the signs of optical rotations compare closely for synthetic frondosin B and natural frondosin B, we conclude that (+)-frondosin exists as the *R*-enantiomer.

Summary

In summary, several interrelated routes to racemic frondosin B have been developed. The intermolecular Diels−Alder reaction of nitroethylene and **42** was the most effective way that we found to introduce the dimethylcyclohexane A ring with regiochemical definition. Subsequently, a route to the natural antipode of frondosin B was developed. An unexpectedly difficult obstacle in this synthesis was that of maintaining the enantioenrichment of the secondary methyl center of compound **33**. Eventually, this problem was solved and frondosin B was obtained in 84% ee. The route, which was followed, establishes the absolute configuration of frondosin B as *R*. It is appropriate to note that in various anti-HIV evaluations, the racemic, fully synthetic frondosin B did not meaningfully suppress viral growth. Thus, the future of frondosin B in AIDS therapy, at least, does not appear to be promising. Further biological studies on frondosin B are currently underway.

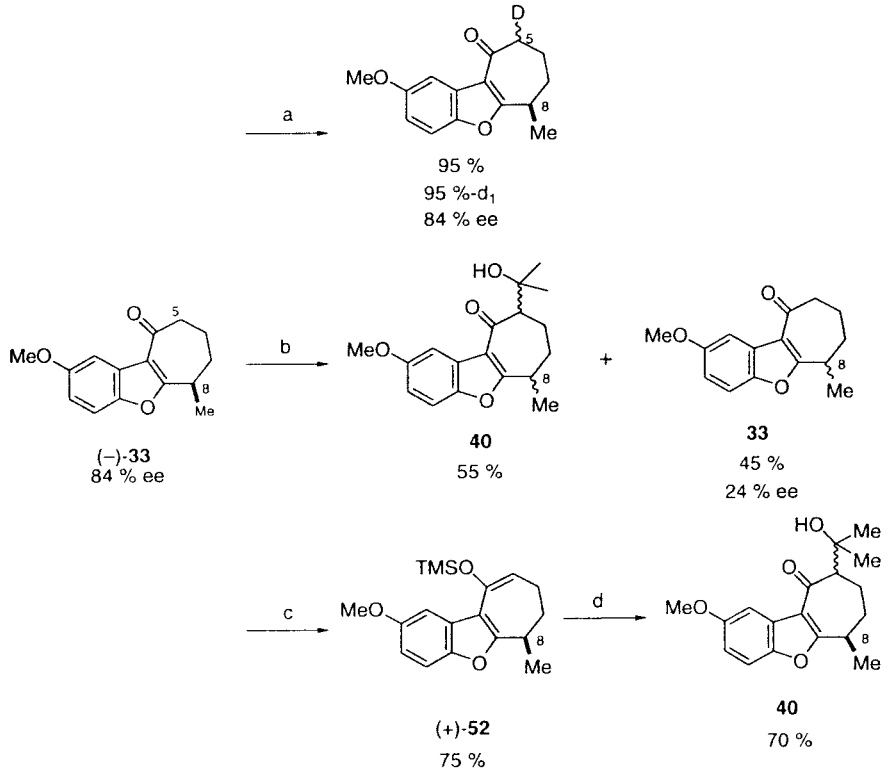
Experimental Section

Preparation of Olefin 37. To a stirred solution of phosphonium salt **36** (16.5 g, 36.1 mmol) in THF (35 mL) was added NaHMDS (1.0 M solution in THF, 32 mL, 32 mmol) at 0 °C. After 30 min at 0 °C, methyl ketone **35** (3.7723 g, 21.2 mmol) in THF (20 + 10 mL) was added to the ylide via cannula, and the resultant solution was stirred at 0 °C for 30 min and at room temperature for 1.5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with EtOAc (400 mL). The organic layer was washed with H_2O and brine, dried (Na_2SO_4), and concentrated. Flash column chromatography (10−20% EtOAc−hexane) gave olefin **37** as a 3:2 mixture of *Z*:*E* isomers (5.25 g, 86%): IR (film) 2980, 1731, 1474, 1208, 1029 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.33 (d, J = 8.9 Hz, 3/5 H), 7.28 (d, J = 8.9 Hz, 2/5 H), 6.99 (d, J = 2.6 Hz, 3/5 H), 6.96 (d, J = 2.6 Hz, 2/5 H), 6.86 (dd, J = 8.9 Hz, 2.6 Hz, 3/5 H), 6.82 (dd, J = 8.9 Hz, 2.6 Hz, 2/5 H), 6.57 (s, 3/5 H), 6.49 (s, 2/5 H), 6.29 (td, J = 7.3 Hz, 1.2 Hz, 2/5 H), 5.57 (td, J = 7.3 Hz, 1.2 Hz, 3/5 H), 4.13 (q, J = 7.1 Hz, 2H), 3.83 (s, 9/5 H), 3.82 (s, 6/5 H), 2.86 (q, J = 7.2 Hz, 6/5 H), 2.57 (q, J = 7.3 Hz, 4/5 H), 2.48 (t, J = 7.6 Hz, 2H), 2.08 (d, J = 1.1 Hz, 9/5 H), 2.03 (d, J = 1.1 Hz, 6/5 H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.2, 173.0, 158.4, 157.4, 155.9, 155.8, 149.5, 149.4, 129.7, 129.6, 128.9, 126.5, 125.8, 125.3, 112.9, 112.5, 111.4, 111.1, 104.8, 103.3, 103.1, 101.7, 60.4, 60.3, 55.9, 34.5, 33.9, 25.0, 23.7, 21.8, 14.2, 13.3; HRMS (FAB) $[M]^+$ calcd for $C_{17}H_{20}O_4$, 288.1362; found, 288.1355.

Carboxylic Acid 34. A solution of olefin **37** (2.07 g, 7.19 mmol) and Pd/C (400 mg) in EtOAc (50 mL) was stirred at room temperature under hydrogen for 2h. The mixture was filtered through Celite and concentrated to give the crude ester, which was used in the next reaction

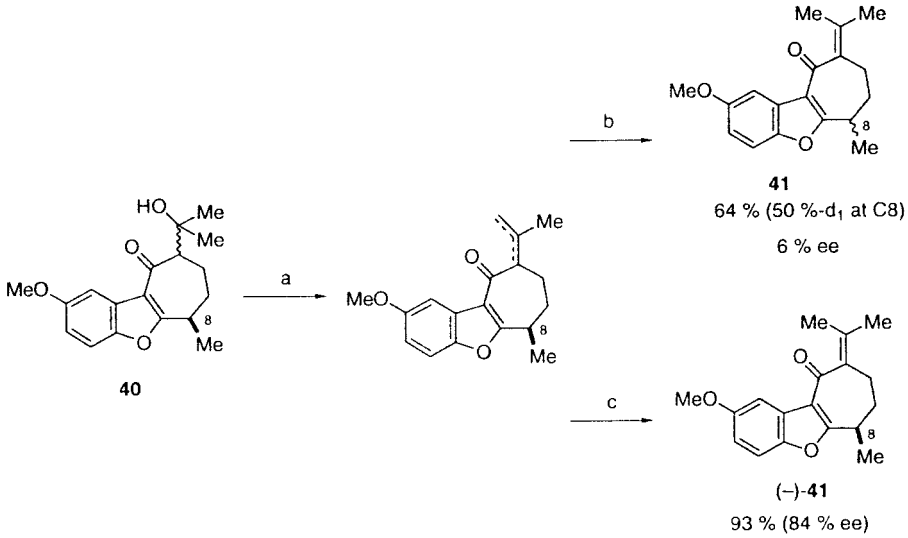
(51) For another example of this type of Pd(II)-catalyzed isomerization, see: Whang, K.; Cooke, R. J.; Okay, G.; Cha, J. K. *J. Am. Chem. Soc.* **1990**, *112*, 8985.

Scheme 12[a]



[a] Reagents and conditions: (a) 1.1 equiv LiHMDS, THF, −40 °C, 0.5 h; MeOD, −40 °C; (b) 1.5 equivs LiHMDS, THF, −40 °C, 0.5 h; 1.5 equivs $ZnCl_2$, Et_2O, −40 °C, 10 min; 2.0 equivs Me_2CO, −40 °C, 0.5 h; (c) 3.0 equivs LiHMDS, 3.0 equivs TMSCl, THF, −40 °C, 1 h; (d) 1.1 equivs $TiCl_4$, 2.0 equivs Me_2CO, 0 °C, 1 h.

Scheme 13[a]



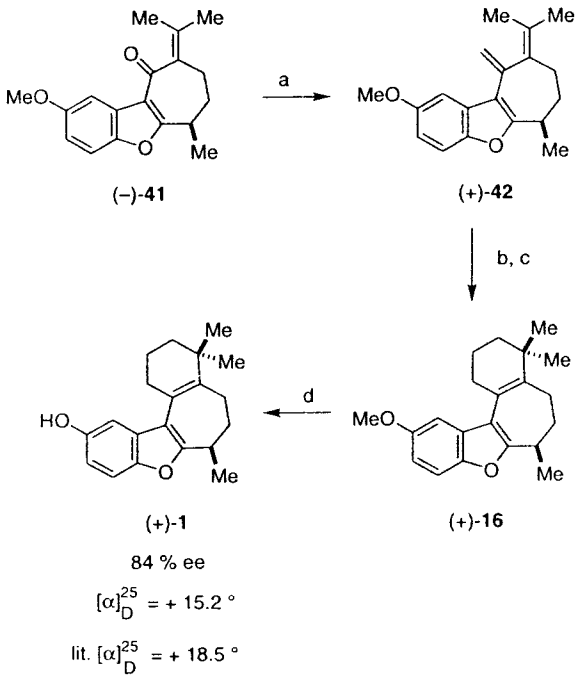
[a] Reagents and conditions: (a) MsCl, NEt_3, CH_2Cl_2, 0 °C; (b) MeONa, MeOD(H), 0 °C; (c) $PdCl_2(MeCN)_2$, PhH, reflux, 93%.

without further purification: IR (film) 2967, 1732, 1476, 1205, 1179 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.28 (d, J = 8.9 Hz, 1H), 6.95 (d, J = 2.6 Hz, 1H), 6.79 (dd, J = 8.9 Hz, 2.6 Hz, 1H), 6.32 (s, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.81 (s, 3H), 2.89−2.94 (m, 1H), 2.29 (t, J = 7.2 Hz, 2H), 1.75−1.80 (m, 1H), 1.58−1.67 (m, 3H), 1.31 (d, J = 7.0 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.5, 164.0, 155.6, 149.4, 129.3, 111.4, 111.1, 103.1, 101.1, 60.3, 55.9, 34.7, 34.2, 33.4, 22.5, 18.9, 14.2.

A solution of the above ester in THF−MeOH−H_2O (4:1:1, 60 mL) was treated with LiOH·H_2O (930 mg, 22.2 mmol), and the mixture was stirred at room temperature for 2 h. The solution was acidified with 1N HCl (45 mL) and extracted with $CHCl_3$ (100 mL × 2, 50 mL × 2). Drying (Na_2SO_4), concentration, and flash column chromatography (5−10% MeOH−$CHCl_3$) gave carboxylic acid **34** (1.88 g, 100%): IR (film) 3300−2500, 2935, 1707, 1476, 1205 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.29 (d, J = 8.9 Hz, 1H), 6.96 (d, J = 2.6 Hz, 1H), 6.80 (dd, J = 8.9 Hz, 2.6 Hz, 1H), 6.32 (s, 1H), 3.82 (s, 3H), 2.90−2.96 (m, 1H), 2.35 (t, J = 7.1 Hz, 2H), 1.76−1.85 (m, 1H), 1.60−1.70 (m, 3H), 1.32 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.6, 163.9, 155.7, 149.5, 129.3, 111.5, 111.1, 103.2, 101.1, 55.9, 34.7, 33.9, 33.5, 22.3, 18.9; HRMS (FAB) $[M]^+$ calcd for $C_{15}H_{18}O_4$, 262.1205; found, 262.1203.

(−)-(*R*)-Carboxylic Acid 34. A mixture of benzofuran (−)-**50** (432 mg, 1.56 mmol) and LiOH·H_2O (197 mg, 4.69 mmol) in THF−MeOH−H_2O (4:1:1; 16.5 mL) was stirred at room temperature for 2 h before acidification with 5 mL of 1 N HCl. After typical workup as

Scheme 14[a]



[a] Reagents and conditions: (a) Tebbe reagent, THF, −40 °C, 98%; (b) nitroethylene 2,6-di-*tert*-butylpyridine, PhH, 80 °C, 36 h, 65%; (c) Bu_3SnH, AIBN, PhMe, 110 °C, 4 h, 40%; (d) EtSNa, DMF, 140 °C, 4 h, 78%.

described above and concentration of the organic layers, the crude oil was purified by column chromatography (5% $CHCl_3$−MeOH) to afford 423 mg (100%) of the enantio-enriched carboxylic acid **34**: $[\alpha]^{27}_D$ = −20.6 (*c* 0.795, $CHCl_3$).

Ketone 33. A solution of carboxylic acid **34** (280 mg, 1.07 mmol) in CH_2Cl_2 (6 mL) was treated with $(COCl)_2$ (2.0 M in CH_2Cl_2, 0.80 mL, 1.60 mmol), and the mixture was stirred at room temperature for 30 min and at 40 °C for 30 min. The solution was cooled to −78 °C and was treated with $SnCl_4$ (321 μL, 2.74 mmol). The mixture was stirred at −78 °C for 30 min and warmed to −10 °C, and the stirring was continued for 30 min. The reaction was then quenched with 1N HCl (3 mL). The solution was diluted with EtOAc (50 mL) and washed with 1N HCl, saturated aqueous $NaHCO_3$, and brine. Drying (Na_2SO_4), concentration, and flash column chromatography (20% EtOAc−hexane) gave ketone **33** (175 mg, 67%): IR (film) 2935, 1647, 1559, 1473, 1273 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.74 (d, *J* = 2.7 Hz, 1H), 7.27 (d, *J* = 8.9 Hz, 1H), 6.86 (dd, *J* = 8.9 Hz, 2.7 Hz, 1H), 3.85 (s, 3H), 3.30−3.34 (m, 1H), 2.79 (t, *J* = 6.9 Hz, 2H), 2.16−2.22 (m, 1H), 1.99−2.03 (m, 1H), 1.86−1.90 (m, 1H), 1.75−1.80 (m, 1H), 1.45 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.2, 169.3, 156.9, 148.4, 127.5, 117.1, 113.8, 110.8, 104.8, 55.9, 44.9, 35.7, 33.4, 20.2, 19.8; HRMS (FAB) [M + H]$^+$ calcd for $C_{15}H_{17}O_3$, 245.1178; found, 245.1172.

(−)-(*R*)-Ketone 33. The titled ketone was prepared from (−)-**34** in a similar manner as racemate ketone **33**: $[\alpha]^{27}_D$ = +16.0 (*c* 0.0860, $CHCl_3$). The enantiomeric purity was determined by CSP HPLC (1% *i*-PrOH−hexane at 2.0 mL/min; t_R (major enantiomer) = 7.4 min, t_R (minor enantiomer) = 8.8 min). The enantiomeric purity of the material was determined to be 84% [i.e., enantiomeric ratio (er) = 92:8].

Tertiary Alcohol 40. A solution of LiHMDS (1.0 M solution in THF, 2.4 mL, 2.4 mmol) in THF (3 mL) was cooled to −78 °C, and ketone **33** (479 mg, 1.96 mmol) in THF (2 + 1 + 1 mL) was added to this solution. The mixture was stirred at −78 °C for 20 min and at −40 °C for 20 min. To this solution was added $ZnCl_2$ (1.0 M in Et_2O, 2.4 mL, 2.4 mmol) at −40 °C, and the resultant mixture was stirred at the same temperature for 10 min. This solution was treated with acetone (350 μL, 4.77 mmol) and stirred at −40 °C for 20 min. The reaction mixture was quenched with H_2O; diluted with EtOAc (80 mL); and washed with H_2O, saturated aqueous $NaHCO_3$, and brine. Drying (Na_2SO_4), concentration, and flash column chromatography (10−30% EtOAc−hexane) gave tertiary alcohol **40** as a 1:2.5 mixture of isomers (504 mg, 85%), along with recovered starting material **33** (54.4 mg, 11%): IR (film) 3446, 2968, 1618, 1473, 1177 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.61 (d, *J* = 2.6 Hz, 2/7 H), 7.56 (d, *J* = 2.6 Hz, 5/7 H), 7.32 (d, *J* = 8.8 Hz, 2/7 H), 7.30 (d, *J* = 8.8 Hz, 5/7 H), 6.89 (dd, *J* = 8.8 Hz, 2.6 Hz, 1H), 5.85 (br s, 5/7 H), 4.80 (br s, 2/7 H), 3.87 (s, 6/7 H), 3.86 (s, 15/7 H), 3.30 (m, 2/7 H), 3.23 (m, 5/7 H), 2.77 (dd, *J* = 11.2 Hz, 4.8 Hz, 5/7H), 2.71 (dd, *J* = 11.3 Hz, 3.8 Hz, 2/7H), 2.24−2.30 (m, 2/7 H), 2.10−2.19 (m, 2/7 H), 1.75−1.80 (m, 4/7 H), 1.56−1.61 (m, 10/7 H), 1.50 (d, *J* = 7.0 Hz, 6/7 H), 1.39 (d, *J* = 7.0 Hz, 15/7 H), 1.25 (s, 27/7 H), 1.07 (s, 15/7 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 204.5, 202.4, 169.8, 169.3, 157.1, 148.7, 148.4, 133.3, 127.0, 126.9, 118.2, 117.8, 114.04, 114.00, 111.2, 111.1, 104.4, 104.1, 73.7, 73.0, 63.5, 63.3, 60.3, 55.96, 55.92, 37.0, 33.3, 32.1, 32.0, 28.9, 28.8, 25.5, 25.1, 24.3, 22.4, 20.2, 17.9; HRMS (FAB) [M + H]$^+$ calcd for $C_{18}H_{23}O_4$, 303.1596; found, 303.1589.

Tertiary Alcohol 40 from (+)-(*R*)−Silyl Enol Ether 52. A solution of 60.1 mg (0.190 mmol) of (+)−(*R*)-silyl enol ether **52** in 0.80 mL of CH_2Cl_2 was added dropwise to a solution (0 °C) of 23.0 μL (0.227 mmol) of titanium (IV) chloride and 15.0 μL (0.204 mmol) of acetone in 0.8 mL of CH_2Cl_2. The resulting orange-red solution was stirred at 0 °C for 1 h, cooled to −40 °C, and quenched with 1 mL of water. The mixture was warmed, the layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated via rotary evaporation. Column chromatography (10−20% EtOAc−hexanes) of the crude residue afforded 39.6 mg (69%) of the titled compound as well as 5.7 mg (12%) of (−)-(*R*)-ketone **33**. CSP HPLC analysis showed that the recovered ketone **33** had an ee of 84% (er, 92:8).

Olefin 41. A solution of tertiary alcohol **40** (55.5 mg, 0.183 mmol) and Et_3N (260 μL, 1.86 mmol) was cooled to 0 °C and treated with methanesulfonyl chloride (71 μL, 0.92 mmol). After being stirred at 0 °C for 1h, the mixture was diluted with EtOAc (20 mL) and washed with H_2O and brine. Drying (Na_2SO_4), concentration, and flash column chromatography (10% EtOAc−hexane) gave a 1:1 mixture of olefinic isomers (45.8 mg, 88%), which was used in the next reaction without further purification. A solution of the above olefinic mixture (45.8 mg, 0.161 mmol) in MeOH (2 mL) was cooled to 0 °C and treated with NaOMe (25 wt % in MeOH, 100 μL, 0.460 mmol). After being stirred at 0 °C for 4 h, the solution was acidified with Dowex 50-X8 and filtered. Concentration and flash column chromatography (10% EtOAc−hexane) gave olefin **41** (43.9 mg, 96%): IR (film) 2934, 1650, 1626, 1557, 1473 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.76 (d, *J* = 2.7 Hz, 1H), 7.31 (d, *J* = 8.9 Hz, 1H), 6.87 (dd, *J* = 8.9 Hz, 2.7 Hz, 1H), 3.87 (s, 3H), 3.25−3.31 (m, 1H), 2.61 (ddd, *J* = 14.7 Hz, 5.4 Hz, 5.4 Hz, 1H), 2.37 (ddd, *J* = 14.7 Hz, 9.5 Hz, 6.1 Hz, 1H), 2.20−2.26 (m, 1H), 2.03 (s, 3H), 1.89 (s, 3H), 1.62−1.71 (m, 1H), 1.45 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 193.3, 168.5, 157.0, 148.6, 141.0, 135.3, 127.4, 117.7, 113.7, 111.2, 104.1, 55.9, 33.0, 32.9, 26.3, 22.2, 21.6, 17.9; HRMS (FAB) [M + H]$^+$ calcd for $C_{18}H_{21}O_3$, 285.1491; found, 285.1487.

(−)-(*R*)-Olefin 41. A solution of 128 mg (0.423 mmol) of tertiary alcohol **40**, prepared from (+)-**52**, and 0.165 mL (2.13 mmol) of methanesulfonyl chloride in 4.2 mL of CH_2Cl_2 was cooled to 0 °C and 0.590 mL (4.23 mmol) of triethylamine was added dropwise. The resulting yellow mixture was stirred at 0 °C for 3 h. The mixture was then diluted with 80 mL of EtOAc and washed with 15-mL portions of water; 1 N HCl; saturated, aqueous sodium bicarbonate; and brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography (5% EtOAc−hexanes) to give 42.0 mg (35%) of the desired (−)-(*R*)-olefin **41** and 47.7 mg (40%) of its olefinic isomer. In a separate experiment, the olefinic mixture (7.4 mg, 0.026), generated from dehydration of (−)-**40** as described above, was refluxed for 3 h in 0.45 mL of benzene in the presence of 7.0 mg (0.027 mmol) of bis(acetonitrile) palladium (II) chloride. The benzene was removed under vacuum and the crude residue was purified via column chromatography (5−10% EtOAc−hexane) to give 6.9 mg (93%) of (−)-(*R*)-olefin **41**: $[\alpha]^{27}_D$ = −24.2 (*c* 0.627, $CHCl_3$).

Diene 42. A solution of olefin **41** (183 mg, 0.644 mmol) and pyridine

(130 μL, 1.60 mmol) in THF (8 mL) was cooled to −40 °C and treated with Tebbe reagent (0.5 M in toluene, 3.2 mL, 1.6 mmol). After being stirred at −40 °C for 1h, the reaction mixture was diluted with Et_2O (12 mL), and 15% aqueous NaOH. and solid Na_2SO_4 was added to this mixture. The resulting mixture was stirred at room temperature for 1.5 h and filtered through Celite. Concentration and flash column chromatography (10% EtOAc−hexane) gave diene **42** (176 mg, 97%): IR (film) 2930, 1614, 1474, 1200 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.32 (d, J = 8.9 Hz, 1H), 7.17 (d, J = 2.6 Hz, 1H), 6.81 (dd, J = 8.9 Hz, 2.6 Hz, 1H), 5.55 (d, J = 2.2 Hz, 1H), 5.11 (d, J = 2.2 Hz, 1H), 3.85 (s, 3H), 3.05−3.11 (m, 1H), 2.55−2.60 (m, 1H), 2.42−2.50 (m, 1H), 2.00−2.07 (m, 1H), 1.85−1.91 (m, 1H), 1.80 (s, 3H), 1.70 (s, 3H), 1.33 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.8, 155.9, 149.1, 140.6, 135.7, 128.4, 126.1, 116.2, 114.7, 111.2, 111.1, 103.0, 56.0, 33.8, 31.9, 29.3, 22.3, 19.9, 18.6; HRMS (FAB) $[M + H]^+$ calcd for $C_{19}H_{23}O_2$, 283.1698; found, 283.1696.

(+)−(*R*)-Diene 42. The titled diene was prepared in a similar manner as racemate diene **42**: $[\alpha]^{24}_D$ = +22.0 (*c* 1.26, $CHCl_3$).

Diels−Alder Adduct 43. A solution of diene **42** (313.9 mg, 1.11 mmol), nitroethylene (800 mg, 10.9 mmol) and 2,6-di-*tert*-butylpyridine (110 mg, 0.574 mmol) in benzene (7 mL) was placed in a sealed tube and heated at 80 °C for 36 h. After being cooled to room temperature, the solution was concentrated. Flash column chromatography (5−10% EtOAc−hexane) gave Diels−Alder Adduct **43** as a 5:1 mixture of isomers (311.6 mg, 79%): IR (film) 2970, 1588, 1543, 1473, 1369, 1209 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.31 (d, J = 8.9 Hz, 1/5 H), 7.30 (d, J = 8.9 Hz, 4/5 H), 7.06 (d, J = 2.5 Hz, 4/5 H), 7.05 (d, J = 2.5 Hz, 1/5 H), 6.82 (dd, J = 8.9 Hz, 2.5 Hz, 1H), 4.67 (dd, J = 10.4 Hz, 3.2 Hz, 4/5 H), 4.63 (dd, J = 12.4 Hz, 2.9 Hz, 1/5 H), 3.83 (s, 3H), 3.21 (m, 4/5 H), 3.18 (m, 1/5 H), 2.74−2.76 (m, 2H), 2.21−2.37 (m, 3H), 2.04−2.14 (m, 2H), 1.79−1.83 (m, 1H), 1.38 (d, J = 7.0 Hz, 3H), 1.36 (s, 3/5 H), 1.34 (s, 12/5 H), 1.14 (s, 12/5 H), 1.11 (s, 3/5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) of major isomer δ 160.7, 155.4, 149.0, 140.9, 128.6, 123.9, 115.5, 111.1, 111.0, 104.9, 92.6, 56.1, 39.7, 38.2, 33.4, 27.2, 26.1, 25.4, 23.9, 22.3, 20.1; HRMS (FAB) $[M]^+$ calcd for $C_{21}H_{25}NO_4$, 355.1784; found, 355.1776. (+)-(*R*)-diene **42** was converted to **43** in the same manner as described above.

***O*-Methyl Frondosin B (16).** A solution of Diels−Alder adduct **43** (31.9 mg, 0.0890 mmol), AIBN (15.0 mg, 0.0910 mmol) and *n*-Bu_3SnH (500 μL, 1.85 mmol) in toluene (2 mL) was heated at 110 °C for 1.5 h. After being cooled to room temperature, the solution was concentrated and subjected to flash column chromatography (5% EtOAc−hexane) to afford *O*-methyl frondosin B **16** (16.3 mg, 58%): IR (film) 2927, 1591, 1473, 1204, 1035 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.28 (d, J = 8.8 Hz, 1H), 7.15 (d, J = 2.5 Hz, 1H), 6.79 (dd, J = 8.8 Hz, 2.5 Hz, 1H), 3.83 (s, 3H), 3.15−3.22 (m, 1H), 2.57 (t, J = 5.9 Hz, 2H), 2.09−2.18 (m, 3H), 1.70−1.73 (m, 2H), 1.56−1.64 (m, 3H), 1.34 (d, J = 6.9 Hz, 3H), 1.091 (s, 3H), 1.088 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.0, 155.2, 149.0, 144.4, 129.3, 123.8, 116.6, 110.84, 110.77, 105.3, 56.1, 39.5, 38.7, 35.7, 34.6, 30.5, 29.0, 27.9, 26.1, 20.0, 19.7; HRMS (FAB) $[M + H]^+$ calcd for $C_{21}H_{26}O_2$, 310.1933; found, 310.1928.

(+)−(*R*)-*O*-Methyl Frondosin B (16). The titled compound was prepared in a similar manner as the racemate of *O*-methyl frondosin B (**16**): $[\alpha]^{25}_D$ = +9.6 (*c* 0.355, $CHCl_3$). The enantiomeric purity was determined by CSP HPLC [hexane at 1.0 mL/min; t_R (major enantiomer) = 11.4 min, t_R (minor enantiomer) = 21.9 min]. The enantiomeric purity was determined to be 86% (i.e., er = 93:7).

Frondosin B (1). A solution of EtSH (400 μL, 5.40 mmol) in DMF (3 mL) was cooled to 0 °C and treated with NaH (60% in mineral oil, 204 mg, 5.10 mmol). The solution was stirred at room temperature for 30 min. This NaSEt solution (2.3 mL, ∼3.4 mmol) was added to a solution of *O*-methyl frondosin B **16** (52.6 mg, 0.169 mmol) in DMF (1 mL), and the mixture was heated at 140 °C for 3 h. After being cooled to room temperature, the solution was quenched with saturated aqueous NH_4Cl and diluted with EtOAc (60 mL). The organic layer was washed with H_2O and brine, dried (Na_2SO_4), and concentrated. Flash column chromatography (10% EtOAc−hexane) gave frondosin B **1** (47.3 mg, 94%). IR (film) 3370, 2928, 1620, 1589, 1461, 1374, 1197 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.22 (d, J = 8.7 Hz, 1H), 7.11 (d, J = 2.5 Hz, 1H), 6.70 (dd, J = 8.7 Hz, 2.5 Hz, 1H), 4.81 (s, 1H), 3.13−3.22 (m, 1H), 2.52 (t, J = 5.8 Hz, 2H), 2.05−2.17 (m, 2H), 1.63−1.70 (m, 3H), 1.52−1.57 (m, 3H), 1.34 (d, J = 6.9 Hz, 3H), 1.08 (s, 3H), 1.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.2, 150.7, 149.1, 144.3, 129.6, 123.7, 116.5, 111.1, 110.8, 107.3, 39.5, 38.5, 35.7, 34.7, 30.5, 28.9, 27.9, 26.0, 20.0, 19.7; HRMS (FAB) $[M]^+$ calcd for $C_{20}H_{24}O_2$, 296.1776; found, 296.1784.

(+)−(*R*)-Frondosin B (1). The titled compound was prepared from (+)-*O*-methyl frondosin B **16** in a similar manner as racemate frondosin B (**1**): $[\alpha]^{25}_D$ = +15.2 (*c* 0.125, MeOH). The enantiomeric purity was determined by CSP HPLC [5% *i*-PrOH−hexane at 2.0 mL/min; t_R (major enantiomer) = 3.8 min, t_R (minor enantiomer) = 5.0 min]. The enantiomeric purity of the material was determined to be 84% (i.e., er = 92:8).

(−)-Methyl 5(*S*), 6(*S*)-epoxy-7-hydroxyheptanoate (47). Titanium (IV) isopropoxide (0.380 mL, 1,27 mmol) was added dropwise to a mixture of (+)-diisopropyl-L-tartrate and crushed molecular sieves in 225 mL of CH_2Cl_2 at 5 °C. The mixture was cooled to −20 °C and *tert*-butyl hydroperoxide (3.4 M, 7.70 mL, 26.2 mmol) was added dropwise. The resulting mixture was warmed to −15 °C and methyl 7-hydroxy-5-(*E*)-heptenoate (**46**) was added over a 5-min period. The contents of the flask were stirred at −15 °C for 3 h before the slow addition of cellulose phosphate (−40 °C), which removed the titanium catalyst. The mixture was filtered, and the solid was washed with copious amounts of EtOAc (∼400 mL). The solvent was removed via rotary evaporator, and the crude residue was purified by flash chromatography (20−40−50−60% EtOAc−hexane) to give 1.38 g (63%) of the known epoxide:[40a] $[\alpha]^{27}_D$ = −27.9 (*c* 0.654, $CHCl_3$); IR (film) 3450 (br), 2952, 2871, 1736, 1438, 1255, 1202 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.89 (dd, J = 13.7 Hz, 2.2 Hz, 1H), 3.67 (s, 3H), 1.57−1.66 (m, 2H), 3.63 (dd J = 13.7 Hz, 4.2 Hz, 1H), 2.91−2.97 (m, 2H), 2.38 (t, J = 7.4 Hz, 2H), 2.05 (br s, 1H), 1.77−1.82 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.64, 61.57, 58.26, 55.34, 51.46, 33.33, 30.70, 21.20. Enantiomeric excess was determined by converting epoxy alcohol **45** to its Mosher ester using the general technique.[52] In the event, (−)-(*R*)−Mosher's chloride (53.0 mg, 0.210 mmol) in pyridine (0.1 mL) was added to a solution of 25.8 mg (0.148 mmol) of **45** in pyridine (0.2 mL). After the typical workup, the solution was concentrated under vacuum. ^1H NMR analysis of the crude diastereomeric mixture of the Mosher ester indicated that **45** was formed in 84% ee.

(+)-Methyl 6-*R*, 7-dihydroxy-5*R*-methyl heptanoate (48). A solution of 898 mg (5.15 mmol) of methyl (−)-5(*S*), 6(*S*)-epoxy-7-hydroxyheptanoate (**47**) in 3 mL of CH_2Cl_2 was added dropwise over a 30-min period to a 1.46 M solution of $AlMe_3$ (54.0 mmol) in hexanes−CH_2Cl_2 (2.7:1 by vol) at −78 °C. The resulting white mixture was stirred at −78 °C for 3 days before carefully quenching with 5 mL of saturated, aqueous NaF. The mixture was allowed to warm and was then filtered through a scintered glass funnel. The white aluminum salts were washed with excess EtOAc (250 mL) and extracted with additional EtOAc for 4 days via a Soxhlet extractor. The organic extracts were combined and concentrated under vacuum. The crude residue was purified by flash chromatography (80% EtOAc−hexane) to yield 593 mg (60%) of a clear oil: $[\alpha]^{27}_D$ = +11.2 (*c* 0.580, $CHCl_3$); IR (film) 3414 (br), 2954, 2877, 1738, 1459, 1249, 1171, 1058 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.70−3.74 (m, 1H), 3.68 (s, 3H), 3.49−3.53 (m, 2H), 2.28−2.35 (m, 2H), 1.72−1.75 (m, 1H), 1.53−1.62 (m, 3H), 1.22−1.26 (m, 1H), 0.90 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.36, 75.88, 64.62, 51.56, 35.66, 34.04, 31.75, 21.88, 15.22; MRMS (EI) $[M + H]^+$ *m*/*z* calcd for $C_9H_{18}O_4$, 191.1283; found, 191.1278.

(−)-Methyl 5(*R*)-methyl-6-heptynoate (44). A mixture of methyl (−)-6(*R*), 7-dihydroxy-5(*R*)-methyl heptanoate (1.58 g, 8.30 mmol) and $NaIO_4$ (2.70 g, 12.6 mmol) in 60 mL of THF:H_2O (1:1 v:v) was stirred at 25 °C for 2 h. The volatile components were removed via rotary evaporation, and the aqueous layer was extracted with five 60-mL portions of Et_2O. The ethereal extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to afford crude methyl 5-(*R*)-methyl-6-oxohexanoate, which was immediately used in the next step without further purification. A solution of 1.37 g (9.13 mmol) of

(52) Mosher, H. S.; Dull, D. L.; Dale, J. A. *J. Org. Chem.* **1969**, *34*, 2543.

dimethyl (diazomethyl)phosphonate in 10.0 mL of THF was added to a 0.90 M solution (−78 °C) of potassium *t*-butoxide (9.13 mmol) in THF. The yellow solution was stirred at −78 °C for 5 min and a solution of crude methyl 5-(*R*)-methyl-6-oxohexanoate in 1.5 mL of THF was added dropwise over a 30-min period. Gas evolution was observed within 5 min. The orange mixture was stirred overnight at −50 °C. The orange mixture was concentrated to ∼1 mL and then purified by column chromatography (5% EtOAc−hexane) to give 915 mg (71%) of the volatile alkyne: $[\alpha]^{27}_D = -23.0$ (*c* 0.160, $CHCl_3$); IR (film) 3295, 2970, 2934, 2874, 1740, 1454, 1375, 1292, 1167 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.68 (s, 3H), 2.42−2.48 (m, 1H), 2.34 (t, $J = 7.5$ Hz, 2H), 2.05 (d, $J = 2.3$ Hz, 1H), 1.73−1.86 (m, 2H), 1.20−1.50 (m, 2H), 1.19 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.91, 88.46, 68.54, 51.50, 35.98, 33.76, 25.46, 22.65, 20.87; MRMS (EI) *m*/*z* calcd for $C_9H_{14}O_2$, 154.0994; found, 154.0984.

2-Iodo-4-methoxyphenol (45). A solution of 5.23 g (23.4 mmol) of diethyl carbamic acid (4-methoxyphenyl ester)[53] and 2.10 mL of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (25.7 mmol) in 250 mL of THF was cooled to −78 °C, and 21.0 mL of a 1.20 M solution of *sec*-BuLi (48.4 mmol) in cyclohexane was added dropwise over a 10-min period. The resulting bright yellow solution was stirred at −78 °C for 1.5 h to complete the directed ortho-lithiation and a saturated solution of iodine in THF was added dropwise until an orange color persisted in the reaction mixture. The orange mixture was stirred at −78 °C for 30 min before the addition of 50 mL of 10% aqueous sodium thiosulfate. The cooling bath was then removed and the slurry was allowed to warm to room temperature. The resulting mixture was washed with 50 mL of water, dried ($MgSO_4$), and concentrated under reduced pressure. The crude diethyl carbamic acid (2-iodo-4-methoxyphenyl ester) was used in the next step without purification. The crude diethyl carbamic acid (2-iodo-4-methoxyphenyl ester) was dissolved in 70 mL of 2 N NaOH and 70 mL of MeOH, and the solution was refluxed for 4 days. The solution was cooled and then extracted with three 70-mL portions of Et_2O. The aqueous layer was acidified with concentrated HCl to ∼pH 2 and then extracted with five 70-mL portions of Et_2O. The organic layers that were extracted from the acidic layer were combined, dried (Na_2SO_4), and concentrated under reduced pressure. Flash chromatography (5% EtOAc−0.1% AcOH−hexane) afforded 2.92 g (50% from the diethyl carbamyl ester) of the known[54] iodophenol as a white solid: mp 63.5−64.5 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.19 (d, $J =$ 2.9 Hz), 6.91 (d, $J = 8.9$ Hz, 1H), 6.84 (dd, $J = 8.9$ Hz, 2.9 Hz,1H), 5.01(s, 1H), 3.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.86, 149.14, 122.60, 116.31, 115.09, 85.01, 55.93.

Alkynyl Phenol (51). A dry, one-necked, 50-mL, round-bottomed flask was charged, under argon, with 2-iodo-4-methoxyphenol (**45**; 1.35 g, 5.40 mmol), DMF (16.0 mL), triethylamine (1.50 mL, 10.8 mmol), bis(triphenylphoshpine) palladium (II) chloride (134 mg, 0.191 mmol), and copper (I) iodide (134 mg, 0.704 mmol). The dark brown solution was stirred for 20 min at 25 °C before the addition of methyl 5(*R*)-methyl-6-heptynoate (**47**; 915 mg, 5.93 mmol). The solution was stirred for 24 h at 25 °C and then was quenched with 15 mL of H_2O. The aqueous layer was extracted with EtOAc (3 × 30 mL and 2 × 20 mL). The combined organic extracts were washed with H_2O (5 × 25 mL) and brine (25 mL), dried ($MgSO_4$), and concentrated via rotary evaporation. Flash chromatography (5−10−20% EtOAc−hexane) yielded 1.38 g (93%) of **51** as well as 42.0 mg (3%) of benzofuran **50**: $[\alpha]^{27}_D = -29.0$ (*c* 0.445, $CHCl_3$); IR (film) 3442 (br), 2952, 2873, 1730, 1495, 1274, 1164 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.78−6.87 (m, 3H), 5.62 (s, 1H), 3.75 (s, 3H), 3.70 (s, 3H), 2.74 (six-line pattern, $J = 6.9$ Hz, 1H), 2.39 (t, $J = 7.2$ Hz, 2H), 1.77−1.94 (m, 2H), 1.55−1.61 (m, 2H), 1.30 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.95, 152.87, 150.87, 116.59, 115.40, 115.27, 110.06, 101.19, 75.34, 55.80, 51.63, 36.17, 33.61, 26.62, 22.71, 21.09; MRMS (EI) *m*/*z* calcd for $C_{16}H_{20}O_4$, 276.1362; found, 276.1358. Exploratory reactions between alkyne **44** and iodophenol **45** (Table 1) were conducted in a similar manner as described above using either tetramethylguanidine (Table 1, entry 1) or piperidine (Table 1, entry 2) as an amine base.

(−)-(*R*)-Methyl Ester 50. A dry, one-necked, 50-mL, round-bottomed flask was charged, under argon, with (−)-7-(2-hydroxy-5-methoxy-phenyl)-5(*R*)-methyl-hept-6-ynoic acid methyl ester (**51**) (1.38 g, 4.99 mmol), DMF (16.0 mL), triethylamine (1.40 mL, 10.1 mmol), bis(triphenylphoshpine) palladium (II) chloride (123 mg, 0.175 mmol), and copper (I) iodide (127 mg, 0.667 mmol). The dark brown solution was warmed to 50 °C and stirred for 18 h. The solution was allowed to cool and then was quenched with 15 mL of H_2O. The aqueous layer was extracted with EtOAc (3 × 30 mL and 2 × 20 mL). The combined organic extracts were washed with H_2O (5 × 25 mL) and brine (1 × 25 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography (5−10−20% EtOAc−hexanes gradient) yielded 843 mg (61%) of benzofuran **50** as well as 114 mg (8%) of recovered starting material (**51**): $[\alpha]^{27}_D = -20.2$ (*c* 0.104, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.30 (d, $J = 8.9$ Hz, 1H), 6.97 (d, $J = 2.6$ Hz, 1H), 6.81 (d, $J = 8.9$ Hz, 2.6 Hz, 1H), 6.33 (s, 1H), 3.84 (s, 3H), 3.66 (s, 3H), 2.91−2.96 (m, 1H), 2.31−2.35 (m, 2H), 1.76−1.83 (m, 1H), 1.33 (d, $J = 6.9$ Hz, 3H), 1.61−1.70 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.93, 164.05, 155.70, 149.49, 129.30, 111.47, 111.11, 103.21, 101.09, 55.94, 51.49, 34.79, 33.96, 33.47, 22.56, 18.95; MRMS (EI) *m*/*z* calcd for $C_{16}H_{20}O_4$, 276.1362; found, 276.1352.

(+)−(*R*)-Silyl Enol Ether 52. A mixture of 69.0 mg (0.282 mmol) of (−)-(*R*)-ketone **33**, 0.107 mL (0.843 mmol) of chlorotrimethylsilane, and ∼200 mg of crushed molecular sieves in 1.4 mL of THF was cooled to −40 °C, and 0.860 mL of a 0.98 M solution of LiHMDS (0.843 mmol) was added dropwise. The resulting dark yellow solution was stirred at −40 °C for 1 h before quenching with 2.0 mL of saturated, aqueous, $NaHCO_3$. The layers were separated and the aqueous layer was extracted with three 2-mL portions of EtOAc. The combined organic extracts were washed with 2 mL of brine, dried (Na_2SO_4), and concentrated under vacuum. The crude residue was purified by flash chromatography (20% EtOAc−hexane) to give 66.6 mg (75%) of the silyl enol ether as well as 7.4 mg (11%) of recovered starting material: $[\alpha]^{27}_D = +18.8$ (*c* 1.13, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.47 (dd, $J = 8.9$ Hz, 2.7 Hz, 1H), 7.29 (d, $J = 8.9$, 1H), 6.85 (d, $J = 2.7$ Hz, 1H), 5.28 (t, 6.5 Hz, 1H), 3.86 (s, 3H), 3.32 (six-line pattern, $J =$ 7.0 Hz, 1H), 2.24−2.33 (m, 1H), 2.02−2.06 (m, 1H), 1.61−1.80 (m, 1H), 1.40 (d, $J = 7.0$ Hz, 3H), 0.31 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.48, 148.58, 145.83, 128.34, 113.94, 113.09, 112.42, 111.05, 110.88, 110.68, 109.52, 104.94, 55.83, 35.17, 32.52, 22.38, 20.29, 0.23; MRMS (FAB) *m*/*z* calcd for $C_{18}H_{24}O_3Si$, 316.1495; found, 316.1485.

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Supporting Information Available: Experimental procedures and spectral character not involved in the most specific total synthesis (general method, **1**, **6**−**9**, **11**−**14**, **18**−**21**, **30**, **39**) and ^1H NMR spectral data for compounds (**1**, **16**, **30**, **33**, **34**, **37**, **39**−**43**). This material is available free of charge via the Internet at http://pubs.acs.org.

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